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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/821,710	04/08/2004	Michael Wayne Graham	546322000304	1697

20872 7590 02/08/2005

MORRISON & FOERSTER LLP
425 MARKET STREET
SAN FRANCISCO, CA 94105-2482

EXAMINER	
SULLIVAN, DANIEL M	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 02/08/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/821,710	GRAHAM ET AL.	
	Examiner	Art Unit	
	Daniel M Sullivan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 December 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *44-76* is/are pending in the application.

4a) Of the above claim(s) *62-76* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *44-61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *08 April 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 09/646,807.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/2/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This is the First Office Action on the Merits of the application filed 8 April 2004 as a continuation of US application 10/646,070 filed 22 August 2003, which is a continuation of US application 09/646,807 filed 5 December 2000, which is the US national stage of international application PCT/AU99/00195 filed 19 march 1999, which is a continuation-in-part of US applications 09/100,812 and 09/100,813, both filed 19 June 1998. The preliminary amendments filed 8 April 2004, 29 July 2004 and 15 December 2004 have been entered. Claims 1-43 were originally filed and canceled in the preliminary amendment filed concurrently therewith (8 April amendment). Claims 44-76 were added in the 8 April amendment and claims 44, 61, 62 and 76 were amended in the Paper filed 15 December 2004. Claims 44-76 are presently pending.

Election/Restrictions

Applicant's election with traverse of Group I (claims 44-61) in the reply filed on 15 December 2004 is acknowledged. The traversal is on the ground(s) that it would not be an undue burden to examine the process claims with the product claims at this time. This is not found persuasive because, as stated in the restriction requirement, in the event that the product is not patentable, a determination of whether each method of using the product is patentable over the art is based upon the particulars of the method and not on the product used in the method. Therefore, as the product claims are not allowable, search and examination of the process claims with the product imposes an undue burden on the Office.

The requirement is still deemed proper and is therefore made FINAL.

Claims 62-76 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention. Claims 44-61 are presently under consideration.

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The claims under examination are directed to an isolated nucleic acid molecule comprising an isolated first RNA sequence wherein said first RNA sequence is about 20-100 nucleotides in length. The parent applications contain no support for an RNA sequence limited to about 20-100 nucleotides in length. The closest teaching is found in the second full paragraph on page 8 of the instant application and states, "[n]ormally, a sequence of greater than 20-100 nucleotides should be used, though a sequence of greater than about 200-300 nucleotides would be preferred..." This teaching is the same as the teachings found in the priority documents.

The skilled artisan would not have viewed this statement as teaching that the nucleic acid of the invention should be limited to between about 20-100 nucleotides. In contrast, the statement teaches away from the limitation, actually indicating that the nucleic acids of the

invention should be greater than this range. Thus, the skilled artisan would not have viewed the parent applications as providing descriptive support for the invention as claimed in the instant application. Therefore, the instant application is considered a continuation-in-part of the parent applications and the claims are afforded an effective filing date of 8 April 2004.

Information Disclosure Statement

The information disclosure statement filed 2 August 2004 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each U.S. and foreign patent; each publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. The Examiner was unable to find a copy of the references listed as 33, 34, 35 and 26 [36] in the 09/646,807 application as stated in the transmittal letter and could not find the references listed on the forms PTO-892 or -1449 present in that case.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because: The application was filed with a copy of the declaration executed in the parent and does not reflect the status of the application as a continuation-in-part. MPEP 201.06 states, "[w]here a copy of the oath or declaration from a prior application was filed in a continuation or divisional application, if the examiner determines that new matter is present relative to the prior application, the examiner should so notify the applicant

in the next Office action (preferably the first Office action). The examiner should require: (A) a new oath or declaration along with the surcharge set forth in 37 CFR 1.16(e); and (B) that the application be redesignated as a continuation-in-part."

Specification

The abstract of the disclosure is objected to because portions of the text are missing. It appears that the abstract was not properly positioned during photocopying such that one edge was not copied. Correction is required. See MPEP § 608.01(b).

The disclosure is objected to because of the following informalities:

Pages 57, 60 and 66 disclose sequence data without an accompanying "SEQ ID NO:" referring to the sequence listing.

The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required:

The specification does not provide antecedent basis for the size limitations set forth in claims 44 and 49-55. The specification should be amended to recite these limitations as stated in the originally filed claims.

Appropriate correction is required.

The amendment filed 23 July 2004 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall

introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows:

The sequence listing contains sequences that were not present in the originally filed disclosure (*i.e.*, SEQ ID NO: 1-8 and 12). Although the original filing includes a request to transfer sequence listing from the 10/646,070 application and therefore appears to be relying on the parent application for support, as indicated in the Office letter mailed 22 June 2004, the '070 application does not contain a sequence listing. Therefore, those sequences included in the sequence listing filed 22 June that were not disclosed in the originally filed specification constitute new matter.

Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 44-61 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated nucleic acid molecule comprising a first RNA sequence wherein said first RNA sequence is about 20-100 nucleotides in length and a second RNA sequence wherein said second RNA sequence is complementary to said first RNA sequence, wherein the first nucleic acid molecule is identical to a sequence complementary to a region of a target gene known at the time of filing to be capable of effecting post-transcriptional repression, delay or otherwise reduction of a target gene in a mammalian cell, does not reasonably provide

enablement for the broad scope of any isolated nucleic acid molecule capable of post-transcriptionally repressing, delaying or otherwise reducing expression of a target gene in a mammalian cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided by the inventor; (e) the existence of working examples; (f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art (MPEP 2164.01 (a)).

Nature of the invention and Breadth of the claims: The instant claims encompass an isolated nucleic acid molecule comprising a first RNA sequence wherein said first RNA sequence is about 20-100 nucleotides in length, and wherein the first RNA sequence is at least 80%, 90% or 95% identical to a sequence complementary to a region of any target gene, and a second RNA sequence wherein said second RNA sequence is complementary to said first RNA sequence, wherein said nucleic acid molecule is capable of post-transcriptionally repressing, delaying or otherwise reducing expression of the target gene in a mammalian cell wherein the expression of the target gene is reduced by sequence-specific degradation of a RNA transcript of the target gene by an endogenous system of the mammalian cell.

As the enabling disclosure must teach the skilled artisan how to make and use the full scope of the claimed invention, it is incumbent upon the disclosure to set forth the manner and process of making the genus of nucleic acids within the scope of the claims such that the skilled artisan can make and use what is claimed without undue experimentation.

State of the prior art and level of predictability in the art: First, with regard to making nucleic acids capable of providing a useful level of target gene suppression, the art recognizes that adequate suppression will vary from one target gene to the next and is therefore, unpredictable. Dietz (U.S. Patent No. 5,814,500; made of record on the IDS filed 2 August 2004) teaches that many studies with antisense show that gene expression is suppressed by 80%-90% of the normal level, but that such reduction is not typically sufficient to reduce the biological effect, i.e., 10%-20% expression is sufficient to maintain the biological function sought to be suppressed. Thus it is not a routine matter to design molecules appropriate to induce the degree of inhibition necessary to produce the desired effect. Accordingly, the ability of any given nucleic acid to provide useful post-transcriptional suppression of a gene product cannot be predicted.

Furthermore, the art teaches that, even if useful target gene suppression is demonstrated for an siRNA comprising sequence complementary to a given region of a target gene, the ability of siRNAs comprising sequence complementary to other regions of the same target gene to suppress expression of the same target gene remains unpredictable. Holen *et al.* (2002) *Nucl. Acids Res.* 30:1757-1766 studied the effect of targeting different positions within a target gene on siRNA-induced suppression and found that there was a wide range of efficacy. In particular, Holen *et al.* investigated the accessibility of the region surrounding the target site of the best

siRNA identified therein and concludes, "[s]urprisingly enough, we found that despite the minimal sequence and position differences between these siRNAs, they displayed a wide range of activities (Fig. 2B)" (paragraph bridging pages 1758-1759). Thus, even siRNAs targeted within a narrow segment of the target gene can have dramatically different efficacy.

Similar findings are reported by McManus *et al.* (2002) *J Immunol.* 169: 5754-5760, who concludes, "[o]nly a limited number of the siRNA sequences tested could induce RNAi. For the silencing of most genes, on average one of two candidate siRNAs designed is active in contrast to the one of four and one in five siRNAs tested in targeting CD4 and CD8α" (paragraph bridging the left and right columns on page 5759). Thus, the art teaches that the probability of obtaining an effective siRNA varies from one target gene to the next.

Finally, with regard to enablement for sequences less than 100% identical to a sequence complementary to a region of a target gene, Applicant's own disclosure in the non-patent literature teaches that siRNA is highly specific and even single nucleotide mismatches prevented silencing (see especially Figure 3 and the caption thereto and the second full paragraph on page 239). Thus, it would appear that the vast majority of nucleic acids comprising sequence less than 100% identical to a sequence complementary to a region of a target gene would not have the function recited in the claims.

Amount of direction provided by the inventor and existence of working examples: The instant disclosure provides a general description of methods of introducing nucleic acids into cells and specific examples of constructs intended to be used in the methods to suppress gene expression, however, none of the examples comprise a nucleic acid having the structural properties recited in the claims and, in fact, the specification teaches away from the size

limitations recited in the claims (*Id.*). In addition, Example 6 provides teachings directed to empirical identification of sequences capable of inactivating virus gene expression in mammals and Example 9 provides a prophetic example of inactivation of the α-1,3-galactosyl transferase using the described method and constructs. The specification does not teach a single working example of the claimed invention and is silent with regard to how the unpredictability that existed in the art at the time of filing would be overcome. The instant disclosure essentially describes a nucleic acid construct and method of putting that nucleic acid construct into a cell, and states that a useful degree of repression of gene expression will occur without regard to the many art recognized hurdles that lie between introduction of the nucleic acid construct into the cell and the desired outcome. The disclosure therefore fails to teach the skilled artisan how to make the claimed invention as it is directed to a nucleic acid molecule capable of post-transcriptionally repressing, delaying or otherwise reducing expression of the target gene in a mammalian cell wherein the expression of the target gene is reduced by sequence-specific degradation of a RNA transcript of the target gene by an endogenous system of the mammalian cell.

Relative skill of those in the art and quantity of experimentation needed to make or use the invention: Although the relative level of skill in the art is high, the skilled artisan would not be able to make the full scope of the claimed invention without undue experimentation. The scope of the instant claims is tremendous, encompassing essentially all nucleic acids comprising a first RNA sequence about 20-100 nucleotides in length, wherein the first RNA sequence is at least 80%, 90% or 95% identical to a sequence complementary to a region of any target gene, and a second RNA sequence wherein said second RNA sequence is complementary to said first

RNA sequence so long as the nucleic acid molecule is capable of post-transcriptionally repressing, delaying or otherwise reducing expression of the target gene in a mammalian cell wherein the expression of the target gene is reduced by sequence-specific degradation of a RNA transcript of the target gene by an endogenous system of the mammalian cell. Given the art-recognized unpredictability in identifying operative siRNAs, averaging 50% but less for some target genes (*Id.*), and the expansive scope of the claims, determining which embodiments that were conceived, but not yet made, would be inoperative or operative would require undue experimentation. Although the presence of inoperative embodiments within the scope of the claims does not necessarily render the claims non-enabled, the Federal Circuit Court in *Atlas Powder Co. v. E.I. du Pont de Nemours & Co* (224 USPQ 409, 414; *Id.*) provides, "[o]f course, if the number of inoperative combinations becomes significant, and in effect forces one of ordinary skill in the art to experiment unduly in order to practice the claimed invention, the claims might indeed be invalid" (page 414).

For these reasons, and because the instant disclosure provides no enabling teachings beyond what was already known in the art at the time of filing, the claims are not enabled beyond the scope of the operative embodiments known in the art at the time of filing.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 44-61 are rejected under 35 U.S.C. 102(a) as being anticipated by Harborth *et al.* (publicly available 12 May 2003) *Antisense Nucl. Acid Drug Devel.* 13:83-105.

Harborth *et al.* discloses a series of nucleic acids capable of post transcriptionally repressing delaying or otherwise reducing expression of a target gene in a mammalian cell when introduced into a mammalian cell, wherein the expression of the target gene is reduced by sequence specific degradation of a RNA transcript of the target gene by an endogenous system of a mammalian cell. The nucleic acid molecules of Harborth *et al.* are RNA molecules comprising a first sequence of about 20-100 nucleotides in length, wherein the sequence is 100% identical to a sequence complementary to a region of a target gene and a second RNA sequence wherein said second RNA sequence is complementary to said first RNA sequence (see especially Figures 7 and 9 and the captions thereto). The nucleic acid molecules of Harborth *et al.* anticipate the nucleic acids of the instant claims 44-47 and 61.

Furthermore, Harborth *et al.* teaches nucleic acids comprised at least partially of ribonucleotide analogs according to claim 48 (Figure 7), teaches the molecule wherein the first RNA sequence is 24, 23, 22, 21, 20 or 19 nucleotides in length according to claims 49-54 (Figure 7 and 9), teaches the molecule wherein the first and second RNA sequences are the same length according to claim 56 and 57 (Figure 7) and teaches the molecule wherein the first and second RNA sequences are in the same nucleic acid strand and separated by a nucleic acid stuffer

according to claims 58 and 59 (Figure 9) or wherein the first and second RNA sequences are in separate nucleic acid strands according to claim 60.

Harborth *et al.* teaches nucleic acid molecules comprising each of the limitations of the instant claimed nucleic acid molecules. Therefore, the claims are anticipated by Harborth *et al.*

Claims 44-47, 54 and 56-61 are rejected under 35 U.S.C. 102(b) as being anticipated by McManus *et al.* (2002) *RNA* 8:842-850.

McManus *et al.* discloses a series of nucleic acids capable of post transcriptionally repressing delaying or otherwise reducing expression of a target gene in a mammalian cell when introduced into a mammalian cell, wherein the expression of the target gene is reduced by sequence specific degradation of a RNA transcript of the target gene by an endogenous system of a mammalian cell. The nucleic acid molecules of McManus *et al.* are RNA molecules comprising a first sequence of about 20-100 nucleotides in length, wherein the sequence is 100% identical to a sequence complementary to a region of a target gene (*i.e.*, CD4 and CD8 genes) and a second RNA sequence wherein said second RNA sequence is complementary to said first RNA sequence (see especially Figures 1 and 4 and the captions thereto). The nucleic acid molecules of McManus *et al.* anticipate the nucleic acids of the instant claims 44-47 and 61.

Furthermore, McManus *et al.* teaches the molecule wherein the first RNA sequence is 19 nucleotides in length according to claim 54 (Figure 1), teaches the molecule wherein the first and second RNA sequences are the same length according to claim 56 and 57 (Figure 1) and teaches the molecule wherein the first and second RNA sequences are in the same nucleic acid strand

and separated by a nucleic acid stuffer according to claims 58 and 59 or wherein the first and second RNA sequences are in separate nucleic acid strands according to claim 60 (Figure 1).

McManus *et al.* teaches nucleic acid molecules comprising each of the limitations of the instant claimed nucleic acid molecules. Therefore, the claims are anticipated by McManus *et al.*

Claims 44-47, 49-53, 56, 57, 60 and 61 are rejected under 35 U.S.C. 102(b) as being anticipated by Elbashir *et al.* (2002) *Methods* 26:199-213 (made of record in the IDS filed 2 August 2004).

Elbashir *et al.* discloses a series of nucleic acids capable of post transcriptionally repressing delaying or otherwise reducing expression of a target gene in a mammalian cell when introduced into a mammalian cell, wherein the expression of the target gene is reduced by sequence specific degradation of a RNA transcript of the target gene by an endogenous system of a mammalian cell. The nucleic acid molecules of Elbashir *et al.* are RNA molecules comprising a first sequence of about 20-100 nucleotides in length, wherein the sequence is 100% identical to a sequence complementary to a region of a target gene (*i.e.*, GL2 luciferase) and a second RNA sequence wherein said second RNA sequence is complementary to said first RNA sequence (see especially Figure 5 and the caption thereto). The nucleic acid molecules of Elbashir *et al.* anticipate the nucleic acids of the instant claims 44-47 and 61.

Furthermore, in Figure 1, *inter alia*, Elbashir *et al.* teaches the molecule wherein the first RNA sequence is 24, 23, 22, 21 and 20 nucleotides in length according to claims 49-53, teaches the molecule wherein the first and second RNA sequences are the same length according to

claim 56 and 57 and teaches the molecule wherein the first and second RNA sequences are in separate nucleic acid strands according to claim 60.

Elbashir *et al.* teaches nucleic acid molecules comprising each of the limitations of the instant claimed nucleic acid molecules. Therefore, the claims are anticipated by Elbashir *et al.*

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 571-272-0779. The examiner can normally be reached on Monday through Thursday 6:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Daniel M. Sullivan, Ph.D.
Examiner
Art Unit 1636

Anne-Marie Falk
ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER